THE BEERY FAMILY WHOLE GENOME SEQUENCING SUCCESS

Retta Beery
Patient Advocate, Mother of Twins with Rare Neurologic Disorder
Presidential Commission for the Study of BioEthical Issues
February 2-3, 2012

Zach, Noah, and Alexis Beery
1996

1996-2002

Multiple X-rays

1 surgery (Alexis)

5 EEGs

8 MRIs

8 CT scans

9 Ultrasounds

Countless ER visits

3 Upper GI's

Multiple pediatricians

4 gastroenterologists

6 neurologists

1 pediatric urologist

5 naturopathics

Physical therapists

Occupational therapists

Speech therapists

Blood drawn 200+ times

4 pediatric ophthalmologist

4 orthopedic surgeons

3 pulmonologists

3 ENT

5 allergists

1 oral surgeon

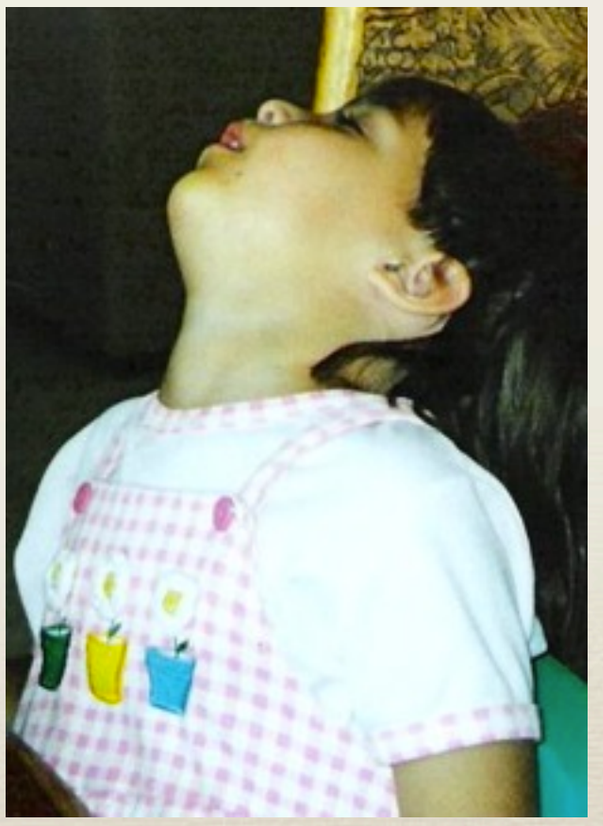
1 genetic doctor

INCORRECT DIAGNOSIS OF CEREBRAL PALSY IN 1998

TREATMENT CENTERED AROUND INCORRECT DIAGNOSIS

FINANCIAL, EMOTIONAL, AND PHYSICAL COSTS MOUNT


GOT YA!
Pokém
Gotta
POWER
RANGERS



Deft Diagnosis

Segawa's Dystonia Mimics Cerebral Palsy but Is Treatable

By THOMAS H. MAUGH II
TIMES SCIENCE WRITER

By successfully treating a little-known disorder that is often misdiagnosed as cerebral palsy, researchers are gaining valuable insight into an entire class of chronic neurologic conditions, including Parkinson's disease.

The disease, known as Segawa's dystonia, may afflict as many as 10,000 people in the United States but often goes unrecognized. Like cerebral palsy, the crippling disorder is marked by tremors and rigidity. But unlike most other neurological disorders, Segawa's is readily treated with small doses of L-dopa—the drug used to treat Parkinson's.

A dramatic example of Segawa's—and of the ability of L-dopa to alleviate it—may be seen in the case of Kimberly Nelson of Trinity, N.C.

When she was 7, Kimberly developed what her mother, Brenda, called a "funny walk. Her balance was not real good and she would fall down frequently."

By the time she was 14, Kimberly had to hold onto walls or another person to walk and could travel only a short distance. She usually walked on her toes to maintain her balance, her head bent distinctly to the left, her left arm had started "turning in" and her left hand often involuntarily clenched into a fist.

Ron and Brenda Nelson took her to hospitals throughout the country. "Every thing they did—tests, CAT scans, myelograms, MRIs—came back normal; there was nothing they could find anywhere," said Brenda Nelson. "We were at a dead end."

After a chance conversation with a physician friend in church, the family visited the National Institutes of Health, where they met neurologist John K. Fink. Fink and his colleagues suspected that Kimberly had Segawa's.

To test their theory, they gave her a tablet of L-dopa, the drug normally used to treat Parkinson's disease that has been used successfully on Segawa's patients for more than 20 years. Brenda recalled that an hour or two later, as the family walked through the NIH lobby on the way to dinner, "She said, 'Look, Dad! I can walk without holding on. I can keep my balance now.' It was like a miracle had taken place in front of our eyes."

That was in December, 1989. Kimberly has been on L-dopa ever since and now has "no symptoms at all." The high school sophomore played on the softball team at school last year, is active in her youth group and last month was inducted into the National Honor Society. In short, she is able to do everything that other girls her age do.

Miraculous as it may seem, Kimberly's recovery is not unusual. Virtually all patients with Segawa's exhibit a similar renaissance when given the drug, and the effects are long-lasting, according to a report in the most recent issue of the journal Neurology. Unfortunately, "the majority of people, including most neurologists, are simply not familiar with it [Segawa's]," said Fink, who is now at the University of Michigan Medical Center in Ann Arbor.

(Similar, dramatic recoveries of comatose patients given L-dopa have been documented by neurologist Oliver Sacks of the New York Department of Health in the book "Awakenings" and in the movie of the same name. Those patients, however, suffered from encephalitis—sleeping sickness—unrelated to Segawa's, and their recovery was only temporary.)

Fink estimates that as many as 10,000 people in the United States may suffer from Segawa's without knowing it, with women about 2½ times more likely to have the genetic disorder than men. In many cases physicians are not able to make any diagnosis. In others, it is mistaken for a psychological problem. But most often it is misdiagnosed as cerebral palsy, he said.

TOM CORELAND / For T

Kimberly Nelson, with friend Lynn Albertson, is now an active sophomore who plays on the high school's softball

more about the unusual disease. "Once we figure this out," he said, "it will be a model for understanding other inherited neurological or psychiatric disorders, such as Parkinson's disease."

Some researchers think Fink's estimates of prevalence may be a little too high. But, noted neurologist Roger C. Duvoisin of the University of Medicine and Dentistry of New Jersey in New Brunswick, "I'm sure there's more of it than we recognize. . . . I often think and wonder what has happened with patients we've missed in the past."

"There are certainly lots of cases, it's just a question of recognition and diagnosis," added neurologist Torbjoern G. Nygaard of the Columbia-Presbyterian Medical Center in New York City, lead author of the Neurology paper.

Many of the symptoms of Segawa's dystonia do mimic cerebral palsy, which usually results from a brain injury before or during birth. An estimated 750,000 Americans suffer from cerebral palsy, for which there is no effective therapy. Leg spasticity inhibiting the ability to walk occurs in both disorders. "Virtually every one of the [Segawa's] patients I've seen had been told he or she had CP," Fink said.

But Segawa's has several unusual characteristics that set it apart from cerebral palsy and other neurological disorders. Most unusual is that the symptoms are usually least severe in the morning, becoming more incapacitating through the course of the day.

Because of this diurnal variation, Segawa's is often mistaken for an emotional problem. "Children get up in the morning, get dressed and walk to school," Fink said. "By midmorning, the school nurse calls to say they are unable to walk. Parents are often told it is an emotional disorder such as separation anxiety or regression."

The other major factor that distinguishes Segawa's from cerebral palsy is that the former often runs in families, while the latter virtually never does.

U.S. researchers have identified more than a dozen large families in which the disorder is common. These families are particularly important in the quest for the cause of the disease because studies of their DNA (deoxyribonucleic acid, the genetic blueprint of life) will eventually enable researchers to find the particular gene that is defective. Such studies of families have been used by other researchers to identify the causes of a variety of genetic disorders, such as muscular

But that solution is far from close. "Right now, we don't even know which chromosome it [the defective gene] is on," Nygaard said.

Cases of Segawa's have been sporadically reported in the medical literature since at least 1947. Duvoisin said, but the first complete description of the condition and its response to L-dopa was produced by neurologist Masaya Segawa of the Segawa Neurological Clinic for Children in Tokyo in 1971. He called it "hereditary progressive dystonia." Segawa "has spent the last two

Search Is On for Segawa's Victims

Neurologist John K. Fink is searching for other victims of the disorder, and constantly flies around the country to visit patients who can't come to see him. Fink asks that people who think they or a family member have the disease write to him. He will send them information about the disease and where to go for an evaluation.

His address is:
J. K. Fink MD
Neuroscience Laboratory Building
1103 E. Huron Street
Ann Arbor, MI 43104-1687

decades going to meetings around the world and talking about his patients," Nygaard said, and his name has thus become closely associated with the disorder.

Dystonia is a neurological disorder characterized by powerful, involuntary muscle spasms that jerk parts of the body into unusual postures. Between 100,000 and 200,000 people in the United States suffer from dystonia, according to UCLA neurologist Charles Markham, medical director of the Dystonia Research Foundation. Segawa's, which may account for no more than a few percent of all dystonia cases, is the only form of the disorder that responds to L-dopa.

Researchers have identified the approximate location of the genetic defect that causes the most common form of dystonia. But researchers have shown that that gene, located on chromosome 9, is not the cause of Segawa's dystonia.

the brain are apparently very
Victims of the disorder show no
abnormalities and studies conduc
neurologist Donald Calne of the U
sity of British Columbia in Van
with positron emission tomog
show no difference in brain
between Segawa's patients and h
individuals.

But as is the case with Parki
victims, there is a deficiency of
mine in the brains of Segawa's pa
Dopamine is a neurotransmitter,
hormone that is involved in the
of muscle activity by brain cell
deficient to a much greater ext
patients with Parkinson's disease
the amount of L-dopa require
Segawa's is only about one-fif
amount required for Parkinson's.

Nevertheless, researchers b
that similar mechanisms may
work in the two diseases and tha
findings on Segawa's may lead
treatments for Parkinson's as we
at this stage, Fink said, it wo
premature to speculate what
treatments might be.

In the Neurology paper, Nygaa
neurologists Stanley Fahn of Co
and C. David Marsden of The N
Hospital in London report on stu
66 patients with Segawa's. The m
61 of the patients, showed no re
symptoms after as long as 22 y
treatment with L-dopa.

Four men and one woman s
some "wearing off," a less sa
tory response to the drug, after U
few years of therapy. Nygaard
lated that these five did not hav
Segawa's, but may have had a
Parkinson's disease.

Research also has shown th
brains of Segawa's victims are d
in biopterin, a chemical that is
sary for the synthesis of dopamin
speculated that the defective gen
blueprint for a protein important
synthesis of biopterin.

While Segawa's dystonia is bo
and rarely diagnosed, patients w
disorder might provide clues to
other disorders. "That's what
hoping," Fink said, "that cures
whole class of neurological disea
be discovered."

"If we can find out what
[Segawa's]," said neurologist M
Brin of Columbia, "it may g
insight into what causes dyst
general and why some people
Parkinson's. . . . We're always
for insights into the cause

"Segawa's Dystonia Mimics Cerebral Palsy but is Treatable"
Times Science, April 8, 1991

Alexis - 2009-2010

7 emergency room visits

7 chest x-rays

23 blood draws

2 MRIs

CT scan

17 Pediatrician Visits

2 ENTs

2 Pulmonologists

3 Allergists

1 Gastroenterologist

3 Neurologists

1 Endoscopy

2 (24 hour) Monitors

Countless testing done by each specialist

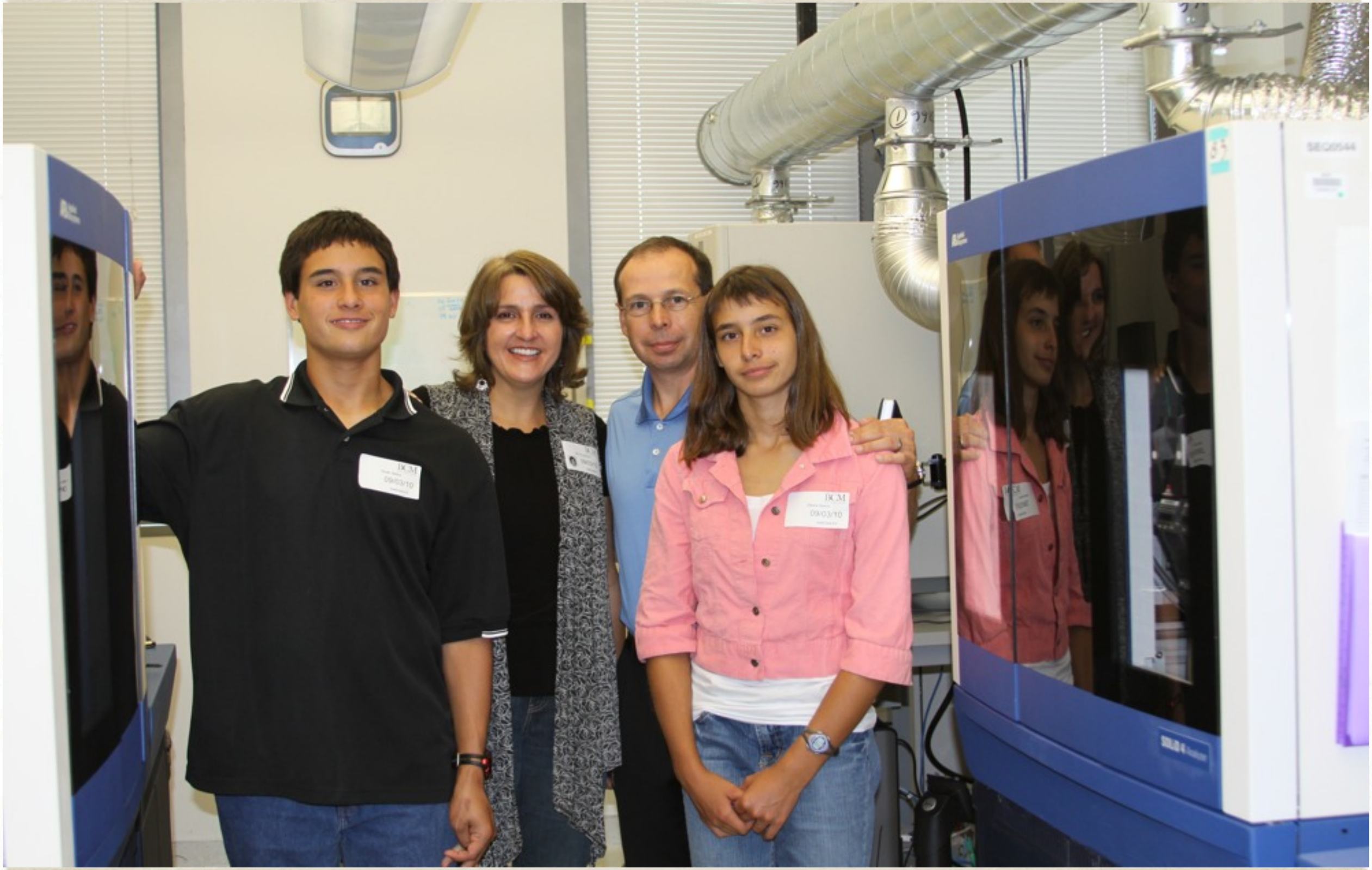
No Answers

Physical Cost

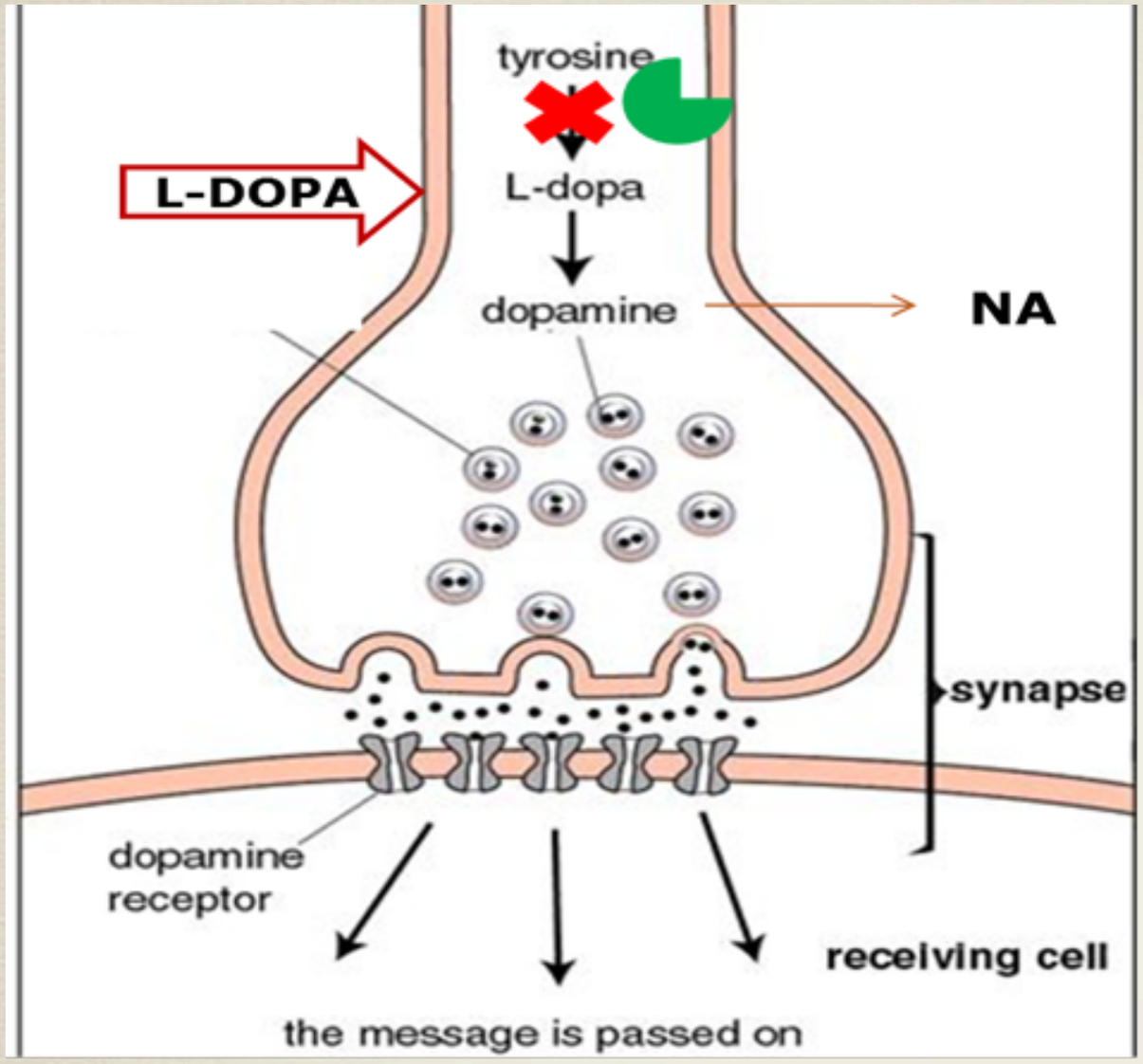
Emotional Cost

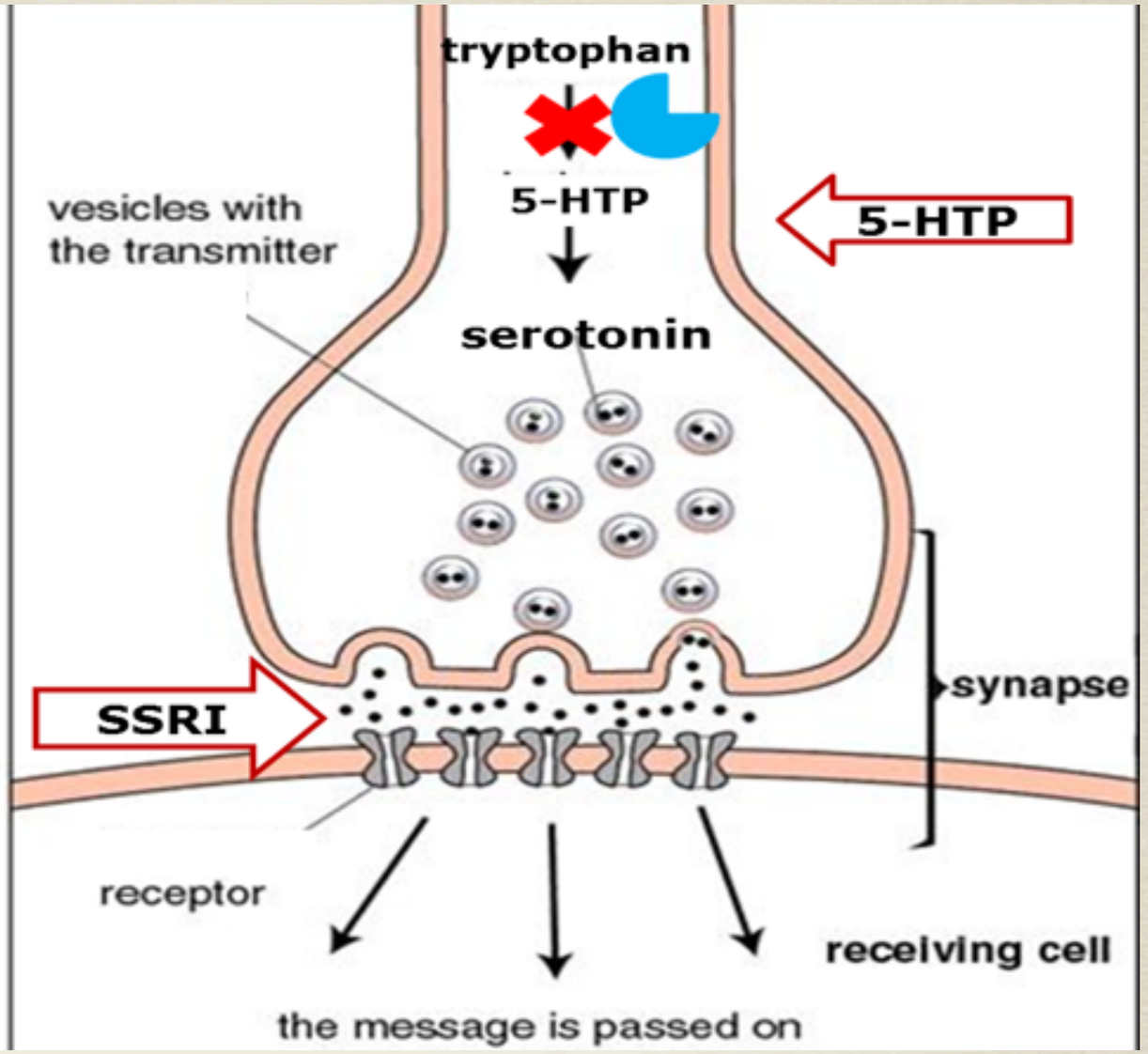
Financial Cost

Struggling to Keep Alexis Breathing while Waiting for Answers



The Genetic Findings





Dopamine Responsive Dystonia in the Beery family is caused by mutations in Sepiopterin Reductase gene

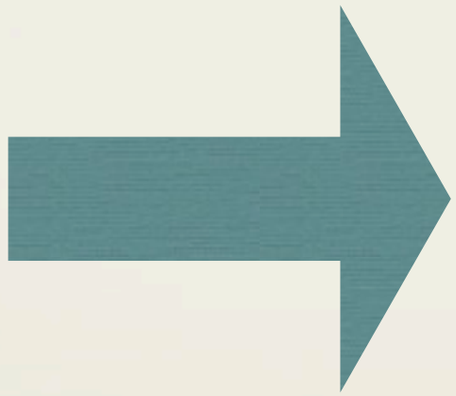
Two hits (mutations) were found in DNA samples coming from Alexis and Noah: K251X and R150G

Whole Genome Sequencing

Consent Forms

Blood Draws

Gathering Information



Definitive, Complete Diagnosis for Noah and Alexis

Additional Therapy Resulting in Breath for Alexis and Higher Function for Noah

New Life for our Family

Alexis Misdiagnosed

Alexis after Whole Genome Sequencing